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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/446,402	12/20/99	BLACK JR.	C 5722-2

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ALSTON & BIRD LLP
P O DRAWER 34009
CHARLOTTE NC 28234-4009

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EXAMINER	
MCGARRY,S	
ART UNIT	PAPER NUMBER
1635	4

DATE MAILED: 12/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/446,402	BLACK JR., CHARLES ALLEN	
	Examiner	Art Unit	
	Sean McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

The instant application discloses sequences in Figure 7 and on page 8, for example, that do not have sequence identifiers. A full response to the instant Official Action requires compliance with the requirements of 37 CFR 1.821 through 1.825.

2. Claim 15 is objected to because of the following informalities: After "5'" on line two there is a period which appears to be a typographical error. Appropriate correction is required.

3. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 5 recite ". . . a second antisense strand bound to the flanking sequence wherein said second strand corresponds to an antisense oligonucleotide to a target molecule." This language is unclear for the following reasons.

There is no antecedent basis for "a second antisense strand" or "said second strand".

It is unclear in the context of the claim what is intended with the term "corresponds". Is it intended to mean that the "said second strand" is similar to an undefined target molecule, for example?

Claim 10 recites ". . . a second antisense strand bound the flanking sequence wherein said second strand corresponds to an antisense oligonucleotide to a target molecule."

There is no antecedent basis for "a second antisense strand" or "said second strand".

It is unclear in the context of the claim what is intended with the term "corresponds". Is it intended to mean that the "said second strand" is similar to an undefined target molecule, for example? Further, does the "a target" on line 9 relate? To the "a target" on line 2?

The claim appears to be missing "to" between "bound" and "the".

Claim 10 recites "marked" on line 3. This apparent typographical error renders the claim unclear.

Claim 14 recites ". . . a second antisense strand bound the flanking sequence wherein said second strand corresponds to an antisense oligonucleotide to a target molecule specific to said organ."

There is no antecedent basis for "a second antisense strand" or "said second strand".

It is unclear in the context of the claim what is intended with the term "corresponds". Is it intended to mean that the "said second strand" is similar to an undefined target molecule, for example?

Claims 3 and 12 recite ". . . wherein said protein of interest encodes a toxin." It is unclear how a protein can encode a toxin.

Claim 4 recites ". . . wherein said target comprises an oligonucleotide which is unique to neoplastic cells" It is unclear what is intended with this limitation. For example, is the target sequence altered to add an oligonucleotide or does the target comprise a unique sequence?

Claims 2, 6-9, 11, and 13 are rejected as they depend from those claims addressed above.

4. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is drawn to "masked expression cassettes" for use in therapies, regulating the expression of a gene to be expressed at a certain time or any instance where it is desirable to regulate gene expression. The instant specification does not provide an adequate written description that would indicate that at the time the application was filed, applicant had possession of the claimed invention. For example the instant invention does not describe how one would maintain such a construct since there is no disclosure of how the "cassette" could be reversibly linked such that it would function as asserted. For example, the specification discusses a RNA complexed with an oligonucleotide that dissociates in the presence of a target molecule which dissociation allows the expression of a gene of interest encoded by the RNA. How does one keep the oligonucleotide associated with the RNA such that the target molecule causes its release? How is this done in storage? In a cell? It is well known that hydrogen bonding is a transient association with many factors especially in a cellular environment that affect such associations.

5. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention is drawn to "masked expression cassettes" and methods of use thereof such as in therapies, in "regulating the expression of a gene to be expressed at a certain time" or in "any instance where it is desirable to regulate gene expression."

The instant specification teaches on how to make the instant compositions but fails to provide adequate guidance for the use thereof.

For example the instant invention does not describe how one would maintain such a construct since there is no guidance of how the "cassette" could be reversibly linked such that it would function as asserted. For example, the specification discusses a RNA complexed with an oligonucleotide that dissociates in the presence of a target molecule which dissociation allows the expression of a gene of interest encoded by the RNA. How does one keep the oligonucleotide associated with the RNA such that the target molecule causes its release? How is this done in storage? In a cell? It is well known that hydrogen bonding is a transient association with many factors especially in a cellular environment that affect such associations. The specification essentially fails to provide guidance or working examples that would show by correlation how one could use the claimed invention such that the cassette becomes "unmasked" and "armed" under any circumstances that would allow the asserted methods of use such as in therapies, in "regulating the expression of a gene to be expressed at a certain time" or in "any instance where it is desirable to regulate gene expression. The specification fails to teach one in the art how to obtain sufficient levels of expression of the protein of interest in the presence of a target molecule such that one could provide a therapy or specifically regulate expression of the protein of interest.

The instant invention includes claims that are drawn to nucleic acid based therapies. The instant invention is drawn to both antisense and gene therapies. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs,

which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*." Anderson [Nature Vol. 392(supp):25-30, 4/98] and Verma et al [Nature Vol. 389:239-242] disclose the general obstacles of gene therapy. The instant specification suffers from antisense specific difficulties as well as those involved in gene delivery and expression in gene therapy. The instant specification does not provide guidance to overcome the obstacles addressed by the references above.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean McGarry whose telephone number is (703) 305-7028.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. Papers should be faxed to Art Unit 1635 via the PTO Technology Center Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see C.F.R. 1.6(d)). The Art Unit 1635 FAX number is (703) 308-4242 or (703) 305-3014. NOTE: If Applicant **does** submit a paper by Fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Sean McGarry

November 30, 2000

SEAN MCGARRY
PATENT EXAMINER

Technology Center 1600